REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 14 and 28 are pending in this application. Claims 19, 26 and 27 are cancelled and claims 14 and 28 are amended herein. Support for the amendments to claims 14 and 28 can be found in the specification at page 15, lines 3-4 and page 15, line 30 - page 16, line 11. No new matter is added.

Applicants thank the Examiner for the courtesy extended during the in-person interview on November 15, 2005. Applicants appreciate the opportunity to discuss the issues in the application.

Applicants are concurrently submitting an Information Disclosure Statement, including the references cited herein, for consideration by the Examiner.

In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Dror Harats under 37 C.F.R. §1.132 and corresponding Appendix 1 ("Harats Declaration").

Rejections under 35 U.S.C. §112, first paragraph

Claims 14, 19, 27 and 28 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner there is no support in the specification as originally filed for the recitation of the phrase, "administration is in a sufficient amount to induce production of IL-10 or TGFβ and to suppress IFN-γ" in claims 14, 27 and 28. *See*, Office Action at page 3. Claims 19 and 27 are cancelled and Applicants have amended claims 14 and 28 to delete "wherein said administration is in a sufficient amount to induce production of IL-10 or TGFβ and to suppress IFN-γ, thereby inhibiting at least one atherosclerosis-related symptom in said subject." Therefore, Applicants submit this rejection is moot and should be withdrawn.

Claims 14, 19, 27 and 28 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner states that the specification does not disclose how to use the claimed method to treat or prevent atherosclerosis in humans using an oral tolerance inducing dosage of modified LDL or OxLDL. *See*, Office Action at pages 3-4.

Claims 19 and 27 are cancelled. The rejection is traversed to the extent that it is applied to the pending claims 14 and 28 as amended herein. The instant claims are not directed to inducing oral tolerance as recitation of "an immunological oral tolerance-inducing" was deleted in Applicants' September 17, 2004 Response to the Examiner's September 9, 2004 Communication.

As discussed at the interview with the Examiner, amended claims 14 and 28 do not recite "oral tolerance inducing" -- rather those claims recite a method of treating atherosclerosis by administering a therapeutically effective amount of an enteric coated composition comprising isolated copper-oxidized LDL or isolated human copper-oxidized LDL and a pharmaceutically acceptable carrier for oral administration.

As discussed at the interview, in view of these claim amendments, the citation of Spack et al. *Expert Opin. On Invest. Drugs*, 6:1715-1727, 1997 ("Spack") and McKown et al., *Arthritis and Rheum.* 42:1204-1208, 1999 ("McKown") are not believed to be relevant to the currently recited invention. The instant invention conformed by additional data generated using the teachings of the specification and reported in the instant Declaration (*See*, Harats Declaration ¶ 8 and Appendix 1), readily demonstrate to one of ordinary skill in the art how to make and use the present invention to treat atherosclerosis by oral administration of an enteric coated composition comprising isolated copper-oxidized LDL or isolated human copper-oxidized LDL.

The use of animal models (*i.e.* murine models) to evaluate the effects of pharmacologic agents on atherosclerosis was well recognized in the art when the instant application was filed (*See, e.g.*, Bocan, *Curr. Pharm. Des.* 4(1):37-52, 1998); and, the LDLR deficient mouse was recognized in the art as a preferred model of atherosclerosis at the time of the instant application. (*See, e.g.*, Ishibashi et al., *J Clin Invest.* 92:883–893, 1993; Lichtman *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 19(8):1938-44, 1999; Maron, R. *et al., FASEB J.* 14:A1199-(Abstr.), 2000). Moreover, mice having targeted inactivation of the apolipoprotein E (ApoE) gene and of the LDLR gene, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. *See*, Harats Declaration ¶ 6.

Applicants provided a working example that demonstrates the successful treatment of atherosclerosis by oral administration of isolated copper-oxidized LDL or isolated human

copper-oxidized LDL. *See*, Specification at, *e.g.*, page 15, lines 20-29; and page 18, line 18 to page 19, line 31. *See*, Harats Declaration ¶ 6.

The Examiner also states that Wouters *et al.*, discloses that the LDLR mouse displays cholesterol metabolic pathways not found in humans and as a consequence "this route can serve as a backup mechanism for lipoprotein clearance in LDLR mice, yielding unforeseen side effects." *See*, Office Action at page 6. Although the LDL-receptor deficient mouse isn't the optimal model for genetic human familial hypercholesterolemia, it is one of the most predictable models for human atherosclerosis and the likelihood of new molecules to work as anti-atherosclerosis drugs in humans is high (*See, e.g.*, Babaei *et al.*, *Cardiovasc Res.* 48(1):158-67, 2000; Burleigh *et al.*, *Biochem Pharmacol.* 70(3):334-42, 2005; Chen *et al.*, *Circulation.* 106(1):20-3, 2002; Collins *et al.*, *Arterioscler Thromb Vasc Biol.* 21(3):365-71, 2001; Cyrus *et al.*, *Circulation.* 107(4):521-3, 2003; Elhage *et al.*, *Am J Pathol.* 167(1):267-74, 2005; Li *et al.*, *J Clin Invest.* 106(4):523-31, 2000; Napoli *et al.*, *Proc Natl Acad Sci U S A.* 99(19):12467-70, 2002). Human atherosclerotic plaques are infiltrated with lymphocytes and display an inflammatory phenotype that includes expression of pro-inflammatory cytokines. In this sense the LDL-receptor deficient mice have plaques similar to those of humans containing a significant number of lymphocytes (*See, e.g.*, Roselaar *et al.*, *Arterioscler Thromb Vasc Biol.* 16(8):1013-8, 1996). Moreover, therapeutic strategies that apply for atheroprotection in humans are similarly successful in LDL receptor deficient mice and may not be so in ApoE knockout mice (*See, e.g.*, Wang *et al.*, *Atherosclerosis.* 162(1): 23-31, 2002). These findings indicate that plaques developing in LDL receptor deficient mice may be more relevant to human atherosclerosis than other non-human models and is one of the most widely employed models for drug development in the field of atherosclerosis. *See*, Harats Declaration ¶ 6.

The Examiner states that there is no disclosure in the specification as to what doses would be used to induce the functional parameters recited in the claim which are related to properties of the oral tolerance induction mechanism. *See*, Office Action at page 5. The instant claims are not directed to inducing oral tolerance but rather are directed to a method of treating atherosclerosis by oral administration of an enteric coated composition comprising isolated copper-oxidized LDL or isolated human copper-oxidized LDL. Applicants have provided working examples that demonstrate the successful treatment of atherosclerosis by oral administration isolated copper-

oxidized LDL or isolated human copper-oxidized LDL in an LDLR deficient mouse and the LDLR deficient mouse is the most art-recognized model of the biochemical and morphological effects of atherosclerosis. Further, the working examples provide a range of concentrations of the composition to treat atherosclerosis (*See, e.g.*, page 18, lines 27-29; page 19, lines 18-19). Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention, would be able to determine the corresponding doses useful in other species, including humans, without undue experimentation. The specification need not disclose what is well known in the art. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). As a footnote, *See*, Harats Declaration ¶ 7-8.

For the above-stated reasons, Applicants submit that amended claims 14 and 28 are enabled, and request this rejection be withdrawn.

Rejection under 35 U.S.C. §102(b)

Claims 27 and 28 are rejected under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 4,874,795 to Yesair ("Yesair"). Claim 27 is cancelled. The rejection is traversed to the extent that it is applied to the amended claim 28.

Applicants have amended claim 28 to delete "human modified low density lipoprotein," as such, amended claim 28 requires that the active component is isolated human copper-oxidized LDL. Yesair neither teaches nor suggests the use of isolated human copper-oxidized LDL and neither teaches nor suggests the treatment of atherosclerosis by oral administration of isolated human copper-oxidized LDL. Applicants submit that claim 28, as amended, is not anticipated by Yesair, and request withdrawal of the present rejection.

Rejection under 35 U.S.C. §103(a)

Claims 14, 19, 27 and 28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sima et al., *11th Int. Symp on Atherosclerosis*, page 227, October 1997 ("Sima") and Hansson et al., *11th Symp on Atherosclerosis*, page 289, October 1997 ("Hansson") in view of U.S. Patent No. 6,541,011 to Punnonen ("Punnonen"). Claims 19 and 27 are cancelled. The rejection is traversed to the extent that it is applied to the amended claims 14 and 28.

Applicants submit that there is no suggestion or motivation to combine Sima and Hansson with Punnonen to reach the present invention. As described *supra*, the present invention is not directed to the induction of oral tolerance but rather the treatment of atherosclerosis by oral administration of isolated OxLDL. As discussed at the interview, the teachings of the primary references, Sima and Hansson, do not suggest any desirability or incentive to orally administer an enteric coated composition comprising isolated copper-oxidized LDL to treat atherosclerosis. In contrast, these references clearly teach that OxLDL contributes to the development of atherosclerosis (*i.e.*, OxLDL is pro-atherosclerotic). *See*, Harats Declaration ¶ 10. Punnonen does not cure these deficiencies of Sima and Hansson as Punnonen is merely general teaching of the induction of oral tolerance, which is not recited in the instant claims.

There is also no expectation of success combining Sima and Hansson with Punnonen to reach the present invention. One of ordinary skill in the art would not reasonably expect the oral administration of an enteric coated composition comprising isolated copper-oxidized LDL to treat atherosclerosis. Specifically, OxLDL is ingested on a daily basis as part of a routine diet and OxLDL is degraded in the gut following ingestion. For this reason, Applicants submit that at the time the application was filed one of ordinary skill in the art would not be motivated to combine Sima and Hansson with Punnonen with a reasonable expectation of success. *See*, Harats Declaration ¶ 10.

Moreover, Applicants submit that one of ordinary skill in the art would not have expected a composition for oral administration comprising isolated OxLDL to be therapeutically effective for treating atherosclerosis.

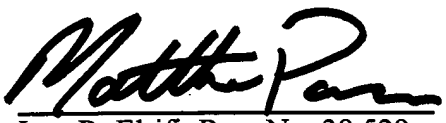
The results described in the specification demonstrate that the composition of the claimed invention (enteric coated composition comprising isolated copper-oxidized LDL and a pharmaceutically acceptable carrier for oral administration) displays the unexpected ability to treat atherosclerosis. *See*, Harats Declaration ¶ 10. These results were not taught or suggested in the art at the time of filing the application (including the teachings of Sima and Hansson) as the state of the art at the time of filing readily recognized OxLDL as a major contributory factor for the development and progression of atherosclerosis.

Applicants respectfully request that the § 103 rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendment and remark, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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